REMARKS

Claims 120-193 are pending in the present application and claims 188-191 stand allowed. By the amendment submitted herewith, claims 120, 128, 130, 131, 135, 140-142, 153, 158-160, 169, 174-176, 186, 187, 192 and 193 are amended to particularly point out and distinctly claim certain embodiments encompassed by the invention.

Support for the present amendments may be found in the application as originally filed, for example, in the specification at page 35, lines 3-18 and 36, lines 3-11 (claims 120, 131, 135, 142, 153, 160, 169, 176, 192, 193); at page 33, line 8 through page 34, line 8 and page 36, lines 12-24 (claims 128, 140, 158, 174); at page 32, lines 16-18 and 22-28, page 33, lines 1-4, page 6, line 9, page 8, line 9, page 10, line 21, page 15, line 10, page 17, line 9 and page 20, line 3 (claims 130, 141, 159, 175, 186; page 44, lines 28-30 and page 45, lines 9-18 (claim 187); and elsewhere. No new matter is introduced by way of the present amendment.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The PTO rejects claims 130, 141, 175 and 186 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the PTO asserts that the structure of formula I in these claims is confusing where it is unclear whether a methyl group or hydrogen is intended as the substituent(s) of "–$(C)_n$–".

Applicants respectfully traverse these grounds for rejection. As disclosed in the specification and recited in the present claims, the instant embodiments are directed in pertinent part to a chemically stable antioxidant compound of formula I in which "–$(C)_n$–" bears substituents R_4 and R_5 that are independently selected from H, hydroxyl, carboxyl, amide, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl and unsubstituted or substituted alkynyl, and wherein n is an integer from 2 to 20. Support for this definition of "–$(C)_n$–" can be found, for example, in the specification at page 32, lines 16-18; page 32, lines 22-28; page 33, lines 1-4; page 6, line 9; page 8, line 9; page 10, line 21; page 15, line 10; page 17, line 9; page 20, line 3; and elsewhere. Therein can be found express teachings as to what the

contemplated structure of "–$(C)_n$–" in formula I can be, including the length and degree of saturation of the carbon chain and the presence of substituents.

Accordingly it is respectfully submitted that the instant claims satisfy the requirements of 35 U.S.C. §112, second paragraph. Reconsideration in view of the present amendments and the Remarks presented here, and withdrawal of the rejections, are respectfully requested.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The PTO rejects claims 128, 140, 158, 169-187 and 193 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. More specifically, the PTO concedes that the specification is enabling for a method of therapy of a patient suffering from or predisposed to Parkinson's disease, Alzheimer's disease, Huntington's Chorea, or Friedreich's Ataxia, as recited. The Examiner then asserts, however, that the specification does not reasonably enable a method of "prophylaxis" for such diseases or a method that comprises administering an antioxidant compound that comprises a "derivative", alleging further that undue experimentation would be required to practice the full scope of encompassed subject matter, and citing the *Wands* factors (*In re Wands*, 8 USPQ2d 1400, CAFC, 1988).

Applicants respectfully traverse these grounds for rejection and submit that based on the instant specification, the skilled person is taught how to make and use the full scope of the claimed embodiments readily and without undue experimentation. Nevertheless, without acquiescence in any rejection, and without prejudice to the prosecution of any surrendered subject matter in a related divisional or continuation application, the instant claims are amended herewith, solely for purposes of advancing prosecution of the present application, to no longer recite "prophylaxis" or "derivative".

It is therefore respectfully submitted that the present claims satisfy all the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejections are therefore requested.

REJECTIONS UNDER 35 U.S.C. §102

Claims 120, 121 and 127 stand rejected under 35 U.S.C. §102 for alleged lack of novelty over Beg et al. (1986 *Pakistan J. Sci. Indust. Res.* 29(3):165-171). More specifically, the PTO asserts that the claimed antioxidant compound is anticipated by the disclosure in the abstract of Beg et al.

Claims 120-185, 192 and 193 stand rejected under 35 U.S.C. §102 for alleged lack of novelty over Murphy et al. (U.S. 6,331,532). In particular, the PTO alleges that the claimed antioxidant compound and its pharmaceutical composition are disclosed by Murphy et al. at columns 2-3 and in the claims.

The rejections are respectfully traversed. The present embodiments are directed in pertinent part to a chemically stable antioxidant compound, comprising a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and an anionic complement for said cationic moiety, wherein the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, and wherein the anionic complement is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion and is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety.

With regard to Beg et al., the subject matter encompassed by claims 120, 121 and 127 can be clearly distinguished. The disclosure of Beg et al. as relied upon by the PTO is limited to compounds having an anionic complement that comprises a chloride ion, whereas the present claims expressly recite that the anion is not a halogen ion and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety. The present application clearly teaches that bromide salts (*i.e.*, a halide salt) of the disclosed antioxidant compounds are unstable, such that the presently claimed embodiments feature an anion that is non-nucleophilic and non-reactive toward the antioxidant moiety, the cationic moiety or the linking moiety (*e.g.*, page 3, lines 17-19; page 4, line 13 through page 5, line 2; page 35, lines 3-

18; page 36, lines 3-11). Beg et al. fail to disclose a non-nucleophilic anion and further fail in any way to suggest that reactivity of the anion with other portions of the compound presents any shortcoming. Beg et al. thus fail to teach or suggest the presently claimed subject matter.

Beg et al. further fail to teach or suggest a compound in which the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, a feature of the presently recited subject matter on which Beg et al. are silent.

Moreover, Beg et al. fail to teach or in any way suggest a compound having as the anion an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate or tetra(perfluorophenyl)borate. It is axiomatic that for the PTO to establish a *prima facie* case of anticipation, each and every element recited by the claim must be disclosed in a single reference. See M.P.E.P. §2131. To be anticipating, the single document must disclose that the elements of the claim are combined in the same way as in the combination recited by the claim. *NetMoney IN vs. VeriSign, Inc.,* 88 USPQ2d 1751 (Fed. Cir. 2008). Where no teaching of the recited anions can be found in Beg et al., it is submitted that no case of anticipation has been established such that the rejections over Beg et al. should be withdrawn.

Turning to Murphy et al., it is respectfully submitted that no case of anticipation has been established where Murphy et al. fail to disclose an antioxidant compound that comprises an anionic complement that is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion, that is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and that does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety.

In this regard, neither in the claims of Murphy et al. nor at columns 2-3, as cited by the PTO, can any disclosure be found pointing to the presently recited anionic complement. Additionally, and as also discussed above with respect to Beg et al., the present application clearly teaches that bromide salts of the disclosed antioxidant compounds are unstable, such that the presently claimed embodiments feature a non-halide anion that is non-nucleophilic and non-reactive toward the antioxidant moiety, the cationic moiety or the linking moiety (*e.g.*, page 3,

lines 17-19; page 4, line 13 through page 5, line 2; page 35, lines 3-18; page 36, lines 3-11). Where the prior art fails to disclose the present antioxidant compounds having such a non-nucleophilic anion, and further fails in any way to suggest that reactivity of the anion with other portions of the compound presents any shortcoming, it is submitted that the presently claimed subject matter has not been anticipated.

Accordingly, applicants submit that the instant claims satisfy the requirements of 35 U.S.C. §102 and respectfully request reconsideration and withdrawal of the rejections.

REJECTIONS FOR DOUBLE PATENTING

A. Claims 120-185, 192 and 193 stand rejected by the PTO under the nonstatutory judicially created doctrine of obviousness-type double patenting, as unpatentable over claims 1-10 of U.S. Pat. No. 7,232,809. Specifically, the PTO asserts that the subject matter encompassed by the present claims, although not identical to that of claims 1-10 of 7,232,809, would have been obvious to a person having ordinary skill in the art for purposes of arriving at the presently claimed compositions and methods.

Applicants respectfully traverse these grounds for rejection and submit that by the amendments submitted herewith, the instant claims are directed to patentably distinct subject matter. In particular, it is submitted that the presently claimed subject matter relates to patentably distinct species, at least some embodiments of which may belong within the genus encompassed by claims 1-10 of U.S. Pat. No. 7,232,809, but for which the PTO fails to establish a *prima facie* case of obviousness. See especially M.P.E.P. §2144.08.

As also discussed above, the present application clearly teaches the unexpected finding that bromide salts of the antioxidant compounds known to the prior art are undesirably unstable (*e.g.*, specification at page 3, line 8 through page 5, line 9; Example 7 at pages 73-79) and thus unsuitable for oral and parenteral pharmaceutical formulations. Only in the present application is it disclosed for the first time that the problem of instability, which is based in nucleophilic attack of other moieties by the halide anionic complement, can be overcome by the use of a non-halogen, non-nitrate, non-reactive pharmaceutically acceptable anion, such as an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate,

hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate or tetra(perfluorophenyl)borate (*e.g.*, page 35, lines 3-18; page 36, lines 3-11; page 3, lines 17-19; page 4, line 13 through page 5, line 2). The specification abundantly discloses previously unexpected stability of the lipophilic cation-linked antioxidants (*e.g.*, Examples 8-10 at pages 79-87) when they are prepared using a non-halogen, non-nitrate, non-reactive pharmaceutically acceptable anion (*e.g.,* an alkyl sulfonate), as recited by the present claims.

Where the prior art fails to disclose the present antioxidant compounds having such a non-nucleophilic anion, and further fails in any way to suggest that reactivity of the anion with other portions of the compound presents any shortcoming, it is submitted that the presently claimed subject matter is neither anticipated nor rendered obvious over the prior art.

Moreover, the instant application also discloses unforeseen advantages of the presently claimed antioxidant compounds over those of the prior art, by presenting *in vivo* data showing that, unlike the instability exhibited by bromide salts of the prior art (discussed at, *e.g.,* page 3, line 8 through page 5, line 9), the instant compounds exhibit significant pharmacokinetic stability with appreciable concentrations persisting in the circulation 24 hours after intravenous or oral administration (*e.g.*, Example 11 at pages 86-91; see also Figure 31 and Table 12). The previously unforeseen advantages of the presently claimed subject matter for pharmaceutical uses are thus clearly disclosed in the instant application and could not have been predicted by the person having ordinary skill in the art, absent the teachings of the present application.

The PTO thus fails to provide evidence or reasoning as to why, given the teachings of U.S. Pat. No. 7,232,809, a person having ordinary skill in the art would have, with the requisite reasonable expectation of success, arrived at the subject matter of the present claims. (*See In re Mayne*, 104 F.3d 1339, 1341-43 (Fed. Cir. 1997), PTO has the burden of showing a *prima facie* case of obviousness). The PTO must show that all of the claimed elements were known in the prior art, that a person skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and that the combination would have yielded nothing more than predictable results to such a skilled person. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385. Additionally, the PTO must show that the person skilled in the art would have had a reasonable expectation of success

in arriving at the claimed subject matter. M.P.E.P. § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)).

In the instant case, it is submitted that the PTO fails to provide evidence or reasoning as to why the skilled person would reasonably have expected *successfully* to combine the recited elements. By alleging otherwise, the PTO impermissibly employs hindsight in view of the present application. "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 550 U.S. __,__, 127 S.Ct. 1727, 82 USPQ2d 1385, 1395 (2007), No. 04-1350 4, 14, (U.S. April 30, 2007).

Furthermore, because the unexpectedly improved stability exhibited by the presently claimed compositions was shown by the applicants to result in improved pharmacokinetic properties *in vivo* (*e.g.*, Example 11 at pages 86-91; see also Figure 31 and Table 12), it is submitted that the patentability of the present subject matter is fully in accord with the holding of the Federal Circuit in *Pfizer Inc. v. Apotex Inc.,* 82 USPQ2d 1321 (Fed. Cir. 2007). There, the Federal Circuit expressly held that:

> [T]he optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where . . . the acid addition salt formulation *has no effect on the therapeutic effectiveness* of the active ingredient and *the prior art heavily suggests the particular anion* used to form the salt. *Pfizer Inc. v. Apotex Inc.,* 82 USPQ2d 1321, 1336 (Fed. Cir. 2007) (emphasis added).

Unlike the situation in *Pfizer v. Apotex*, in the present case the applicants' inventive combination of a pharmaceutically acceptable anion, as recited, with the lipophilic cation-linked antioxidant, clearly *has* an effect on the therapeutic effectiveness of the antioxidant compound, by contributing to its *in vivo* pharmacokinetic properties, as discussed above. Also unlike the situation in *Pfizer v. Apotex*, in the present case the PTO fails to provide any evidence or reasoning whatsoever that the prior art "heavily suggests", with particularity, the use of any of the presently recited anions as the anionic complement according to the present claims.

Accordingly, and in view of the foregoing, it is respectfully submitted that the allegation of nonstatutory obviousness-type double patenting has been obviated. Reconsideration and withdrawal of the rejections are therefore respectfully requested.

B. Claims 120-185 and 192 stand provisionally rejected by the PTO under the nonstatutory judicially created doctrine of double patenting, as unpatentable over claims 120, 122-128 and 130-133 of co-pending Application No. 11/355,518 and claims 88-112 of co-pending Application No. 10/568,654.

Applicants thank the Examiner for making them aware of this provisional double patenting rejection and understand that it may be maintained in each application "as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the applications". M.P.E.P. § 804(I)(B). At such time as this provisional double patenting rejection is the only rejection remaining in the present application, appropriate action will be taken.

C. Claim 134 stands rejected under 35 U.S.C. §101 for alleged double patenting over claim 134 of co-pending Application No. 11/355,518.

Applicants traverse this rejection and respectfully submit that the PTO errs in asserting this rejection as a double patenting rejection. Instead, applicants believe that because Application No. 11/355,518 remains co-pending to the best of applicants' knowledge at this time, a provisional double patent rejection is appropriate. According to M.P.E.P. § 804(II)(A), if the conflicting claims are in another co-pending application, form paragraph 8.31 ("*Rejection, 35 U.S.C. 101, Double Patenting*") should not be used, and instead a provisional double patenting rejection should be made using form paragraph 8.32.

Believing that at most a provisional double patenting rejection is appropriate here, given applicants' belief that Application No. 11/355,518 remains co-pending, it is applicants' understanding that such a provisional double patenting rejection may be maintained in each application "as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the

applications". M.P.E.P. § 804(I)(B). At such time as this provisional double patenting rejection is the only rejection remaining in the present application, appropriate action will be taken. Clarification is respectfully requested if the Examiner believes a provisional double patenting rejection is not appropriate with respect to instant claim 134 and claim 134 of co-pending Application No. 11/355,518.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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